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EXAMINER
MERTZ, PREMA MARIA

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/21/2002 9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/684,383	Hotten et al.
Examiner	**Art Unit**
Prema Mertz	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 1, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *24-28* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *24-28* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I (claims 24-28) in Paper No. 8, 8/1/02 is acknowledged.

Applicants arguments submitted in Paper No. 8, 8/1/02, traversing the restriction requirement, were persuasive. Pending claims 24-28 drawn to both polypeptides of amino acid sequence set forth in SEQ ID NO:2 and 4 will be examined.

Specification

2. here is no "Brief description of the Drawings" heading on pg. 4 prior to the described drawings and is required as set forth in 37 C.F.R. § 1.74.

In the specification, in Figures 3-8, the information about the drawings should not appear on the Figures.

Appropriate correction is requested.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed i.e. a more specific title that would identify the protein being claimed.

Claim rejections-35 U.S.C. 112, first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4a. Claims 24-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 25 encompasses the mature, secreted form of the protein of SEQ ID NO:2 and the mature secreted form of the protein of SEQ ID NO:4. The specification does not disclose the specific sequence of the mature protein recited in claim 25. Page 7, lines 2-4 of the specification discloses that it is possible that the N-terminus of the mature protein is slightly modified i.e. deviates from the sequences shown in SEQ ID NO:2 and 4. Furthermore, on page 8, lines 6-9, recite that the mature part of the MP121 protein "preferably" extends from nucleotide 836 to the stop codon which begins at nucleotide 1184 of the sequence shown I SEQ ID NO:1 . The full-length proteins have the sequence of SEQ ID NO:2 and SEQ ID NO:4 as disclosed in the specification, which is not equivalent to the mature polypeptides recited in claim 25. The skilled artisan cannot envision the detailed chemical structure of the encompassed protein and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The invention is drawn to proteins that occur naturally since they are encoded by naturally occurring polynucleotides. The prior art teaches

neither the encoded proteins nor the recited polynucleotides. It is acknowledged that the skill of the artisan in the molecular biology art is high. It is further acknowledged that in some cases, leader/signal sequences are readily identifiable because of high conservation of certain such sequences across species, families or groups of proteins. Due to the lack of guidance in the prior art and current application, one skilled in the art could not predict if the mature forms of the proteins differ from the full-length form, and if it does, how. The breadth of the claims comes from encompassing proteins, the form of which is not known, and the possibility that more than a single mature protein of SEQ ID NO:2 or SEQ ID NO:4 exists. As written in the claims, the mature form is described as a single compound, however, there is precedence in the prior art for full-length unprocessed proteins to be processed into more than one unique compound. It is not known whether these proteins have only a single precursor form or whether they go through several rounds of signal sequence processing to produce several mature forms as is the case with, for example Neurophysin I and II, which are produced form prepropressophysin and prepro-oxyphysin, respectively (Ganong, 1995, page 220, Fig. 14-11) and pro-opiomelanocortin, which is cleaved during processing to form 8 functional peptides (Creighton, 1984, page 71, Fig. 2-6), or cholecytokinin-pancreozymin (CCK), which undergoes multiple processing steps such that prepro-CCK is processed into many fragments (Ganong, 1995, page 446). There are also cases of protein processing in which the mature form differs from the full-length most significantly in the absences of amino acids internal in the protein (see for example Crieghton, 1984, page 72, Fig. 2-7 of chymotrypsinogen A). Therefore, in the instant case one

cannot predict what the mature form(s) will be. For these reasons, it does not appear that the inventors were in possession of the claimed invention at the time of filing.

4b. Claim 24 and its dependent claims 25-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim 24 is a genus claim. Claim 24, sub-parts (d)-(e) encompass protein variants of SEQ ID NO:2 and 4. The term variant means a protein having one or more amino acid substitutions, deletions, insertions and/or additions made to the protein molecules of amino acid sequences set forth in SEQ ID NO:2 and 4. Claim 25 recites conservative substitutions of SEQ ID NO:2 and 4, which includes natural and non-naturally occurring variants of the claimed proteins. The specification and claims do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the nucleic acid molecule. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification states that these types of changes are routinely done in the art, the specification and claims do not

provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a nucleic acid encoding a protein set forth in SEQ ID NO:2 or 4 alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus of protein molecules.

Therefore only isolated polypeptides comprising the amino acid sequences of SEQ ID NO:2 and 4 but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. As a result, it does not appear that the inventors were in possession of variants of the polypeptides of SEQ ID NO:2 and 4.

4c. Claim 24 and its dependent claim 25-28 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Sections (d) of claim 24 is drawn to polypeptides encoded by a mammalian nucleotide sequence which mammalian proteins differ from the proteins of SEQ ID NO:2 (human) and SEQ ID NO:4 (mouse) due to their origin from other mammals i.e. which are species homologues of the

proteins of SEQ ID NO:2 and 4. Many distinct proteins may share the same activity, say promotion of cell growth, many distinct proteins would have this activity (e.g. many different growth factors, interleukins, hormones, oncogenes). As a result, if one were to isolate a protein from a different species that had the same activity, one could not reasonably predict if the isolated protein was a species homologue of the original protein because one could not determine if the sequence difference between the original and isolate were due to species differences or to the proteins being non-homologous but sharing the same activity. Even though a large number of assays are provided in the specification (see pages 35-38), it would be undue experimentation to conduct every assay in the hopes of identifying a species homologue. Further, the specification provides insufficient guidance to allow one to obtain species homologues using probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species. There is no information about how to identify a suitable probe or primer. Additionally species homologues often display low sequence identity so that identification based solely on sequence similarity is impossible. Under such common circumstances, if one cannot test for the expected activity of the encoded putative species homologue, then it is impossible to identify species homologues. For example in The Cytokine Facts Book (1994), Robin Callard and Andy Gearing. Academic Press Inc. San Diego, CA, the amino acid sequence of IL-2 (interleukin-2) from human compared to mouse differs by 16 amino acids in length (page 39, table) and share only about 60% identity (page 39, "Crossreactivity" section). Based solely on sequence, it would be clearly impossible for one skilled in the art to identify the mouse and human

proteins as species homologues; however, when one is able to compare a known or putative activity (page 39, "Bioassays" section"), identity can be confirmed.

Furthermore, Reeck et al. (line 1-2) point out, ""Homology" has the precise meaning in biology of "having a common evolutionary origin,"...".

It is stated at the top of column 2 that:

A similarity, then, can become a fully documented, simple fact. On the other hand, a common evolutionary origin must usually remain a hypothesis, supported by a set of arguments that might include sequence or three-dimensional similarity. Not all similarity connotes homology but that can be easily overlooked if similarities are called homologies. Thus, in this third case, we can deceive ourselves into thinking we have proved something substantial (evolutionary homology) when, in actuality, we have merely established a simple fact (a similarity, mislabeled as homology). Homology among similar structures is a hypothesis that may be correct or mistaken, but a similarity itself is a fact, however, it is interpreted.

Reeck et al. provided emphasis to the above reasons for not being able to identify, if one is able to isolate candidates, species homologues as claimed because of the lack of guidance and information in the current specification. Thus, at the time the application was filed, polypeptide species homologues (mammalian homologues) of SEQ ID NO:2 and 4 were not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention.

Claims 25-28 are rejected as vague and indefinite insofar as they depend on claim 24 for their limitations.

4d. Claim 24 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the full-length protein of SEQ ID NO:2 or the full-length protein of SEQ ID NO:4, does not reasonably provide enablement for the proteins as recited in claim 24 (d)-(e) which claims protein variants of SEQ ID NO:2 and 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 24 (d)-(e) recites "nucleotide sequence which hybridizes... under stringent conditions". The specification discloses that allelic, degenerate and hybridizing sequences having structural differences due to slight changes in the nucleotide or/and amino acid sequences, and derived from other vertebrates are covered by the present invention (pg. 9, lines 6-12). However, the instant specification fails to describe isolated proteins other than that described in SEQ ID NO:2 and 4. Applicants do not teach which regions of said polypeptides are critical to encode a functional polypeptide. The specification does not provide the requisite examples nor a representative number of different sequences that would allow the skilled artisan to produce a polypeptide other than SEQ ID NO:2 or 4, having the desirable activity (survival of dopaminergic neurons, stimulation of nerve fibre outgrowth from embryonic retina, inhibition of EGF induced DNA synthesis and erythroid differentiation, see pages 35-38), nor does the disclosure provide criteria that explicitly enable such critical features. There is no guidance in the specification as to how one of ordinary skill in the art

would generate polypeptides, other than those exemplified. The issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record.

In summary, the amount of experimentation required for one of ordinary skill in the art to use the claimed invention as described in claim 24 (d)-(e), would be undue. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those nucleotide sequences of the disclosed naturally-occurring nucleic acid encoding the claimed polypeptide, which are required for functional and structural integrity of the claimed polypeptide. It is this additional characterization of the disclosed polypeptide that is required in order to obtain the functional and structural data needed to permit one to produce a polypeptide which meets both the structural and functional requirements of the instant claim that constitutes undue experimentation.

Claim rejections-35 USC § 112, second paragraph

5. Claim 26 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 is vague and indefinite because it recites "cysteine knot motif". The metes and bounds of the claim are unclear. It is suggested that the claims be amended to recite the proteins with a "cysteine knot motif" for which there is a basis in the specification.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6a. Claim 24 is rejected under 35 U.S.C. 102(b) as being anticipated by Forage et al. (1986) .

Forage et al. teach cDNA molecules encoding inhibin sub-units, inhibin being a protein of the TGF-β family (see abstract lines 1-4; page 3092, column 1, last 5 lines and column 2, lines 1-2). A comparison of the amino acid sequence of the inhibin beta-A chain precursor and SEQ ID NO:2 of the instant application is attached to the end of this action (see SEQUENCE COMPARISON "A"). Therefore, the DNA described therein encoding the pentapeptide ser-cys-cys-val-pro-thr (amino acids 215-220 in SEQ ID NO:2), comprises a nucleotide sequence hybridizing with a sequence (SEQ ID NO:1), as is claimed in the present invention. The sequences disclosed in the Forage et al. reference are deemed to meet the limitations of the claimed invention.

6b. Claims 24, 27, are rejected under 35 U.S.C. 102(b) as being anticipated by Mason et al. (U.S. Patent No. 4,798,885).

Mason et al. teach cdNA molecules encoding inhibin, (inhibin being a protein of the TGF-β family), combined with a pharmaceutically acceptable carrier to form a pharmaceutical composition are administered to mammals (see column 3, lines 11-21 and column 32, lines 50-53 of claim 18). Therefore, the DNA described therein (see Figure 6), comprises a nucleotide sequence hybridizing with a sequence (SEQ ID NO:1), as is claimed in the present invention Therefore, the pharmaceutical

composition described in the Mason et al. reference is deemed to meet the limitations of a pharmaceutical composition encompassed by claims 24, 27.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (703) 308-4229. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Prema Mertz

Prema Mertz Ph.D.
Patent Examiner
Art Unit 1646
October 11, 2002